THE USE OF STEROIDS IN THE TREATMENT OF CEREBRAL EDEMA*

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YEAR in and year out the basic investigative problem of the Division of Neurosurgery at the University of Minnesota is related to cerebral edema. One of the early outgrowths of this was the use of sodium fluorescein to distinguish neoplastic lesions from adjacent edematous and normal tissues at the time of surgery.[1] This led to the concept of adding radioactive iodine, making radioactive sodium diiodofluorescein, to use in the detection of intracranial neoplasms with an external counting system.[2] Subsequently this technique has been refined by the use of other gamma-emitting agents and by improvements in the detecting systems. Further studies in this laboratory have been aimed at learning methods to produce edema experimentally and also methods of either preventing the development of edema or combating it once it had developed. We found, as did Broman[3] and others, that one of the most consistent and well-controlled methods of producing edema, or at least of altering the cerebrovascular permeability, was by the intracarotid injection of concentrated doses of Diodrast, Hypaque, or bile salts. With this technique it became possible in the laboratory to alter the permeability consistently in about 70 per cent of animals.[4] Consequently, this was a technique that could be used to help assess the effects of other substances on this altered permeability.

In other studies with experimental brain tumors it was noted that corticoids in large doses seemed to inhibit the growth of the neoplasm. With this knowledge a study was designed to determine the concentration of corticoids in neoplastic and adjacent brain tissues in humans when the corticoid was given into the carotid artery immediately after angiography. The concept was that perhaps the Hypaque used in angiography might alter the permeability so that the corticoid, given immediately thereafter, through the same needle, might get to the neo-

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plasm in fairly high concentrations and possibly alter the growth pattern of the neoplasm. When this was done to an extremely lethargic aphasic and hemiplegic patient with a suspected glioblastoma multiforme, it was observed the following day that the patient was wide awake, alert, and talking. Obviously this could not have had anything to do with the growth of the neoplasm—it could only have altered the surrounding edema. The angiogram was repeated a few days later and the vessels that were displaced by the neoplasm plus the edematous tissue had returned toward their normal position. Similar studies were made on comparable patients with the same pleasant result.[5] The use of the corticoid improved quite dramatically their obtunded clinical condition. With this information a program was then designed to investigate the mode of action of the corticoid and also to try to adapt this drug into clinical use.

Because of its potency and its comparatively low salt-retaining properties dexamethasone (Decadron) was the glucocorticoid selected.

In the laboratory two approaches were made: in the first an attempt was made to correlate the electron microscopic characteristics of edematous cerebral tissue in animals that had been treated with glucocorticoids with those that had not been so treated. Tissue for this study was obtained from: 1) animals in whom edema had been produced experimentally by the placement of hydrophilic psyllium seeds to produce a slowly expanding (intracranial) mass; 2) animals prepared identically to these with the exception that dexamethasone was given according to three schedules: *a*) pretreatment for 48 hours prior to insertion of the psyllium seed, *b*) treatment beginning at the time of insertion, and *c*) treatment after onset of symptoms of brain swelling. In the other part of the study cortical and subcortical tissue was obtained from humans at the time of craniotomy. These were made up of two groups of patients: 1) those judged to have cerebral edema clinically and treated with dexamethasone prior to surgery, and 2) a similar group not treated.

A brief word is necessary concerning the selection of cases. Human cases were studied only if pretreatment symptoms indicated severe edema, and if the response to the corticoid was dramatic. Animal material was used only if pretreatment with the drug eliminated the development of signs and symptoms of edema and/or if later treatment greatly alleviated them.

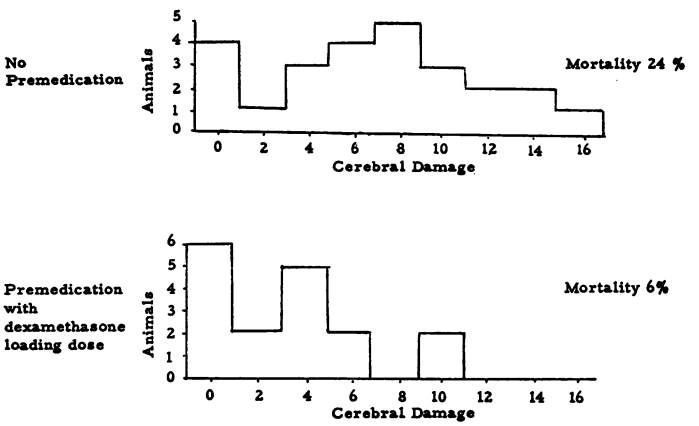

Fig. 1. Graphic summarization of damage produced by intracarotid Hypaque in animals premedicated with dexamethasone compared to a similar group not so premedicated. Dexamethasone decreased the mortality rate as well as the severity of damage (see text).

There was no essential difference between the human material and the animal preparations as far as the electron microscopic appearance of the edema was concerned. The changes found after the dexamethasone administration were qualitatively similar to those observed in edematous tissue, differing only in degree (Figures 1 and 2). This difference, however, was found to be highly significant statistically by measurement analysis of the astrocyte cytoplasm, pericapillary process size, and extracellular space. The clinical states were also found to correlate well with the ultramicroscopic picture, i.e., subjects exhibiting good clinical recovery were found to have brain samples that approach normal, while those less well recovered exhibited more of the features of edema. Dexamethasone seemed to reverse effectively all changes observed in edematous tissue short of tissue necrosis. The cortical changes of edema were observed to respond to therapy before and more completely than those in the white matter.

The second study was designed in an attempt to investigate the protective effect of glucocorticoids on alterations of cerebrovascular permeability produced by the intracarotid injection of large doses of 90 per cent Hypaque under experimental conditions. Because of our previous experience with the permeability of sodium fluorescein this agent was chosen as one method of evaluation of the edema. A measure of cerebral damage was devised that took into account the following

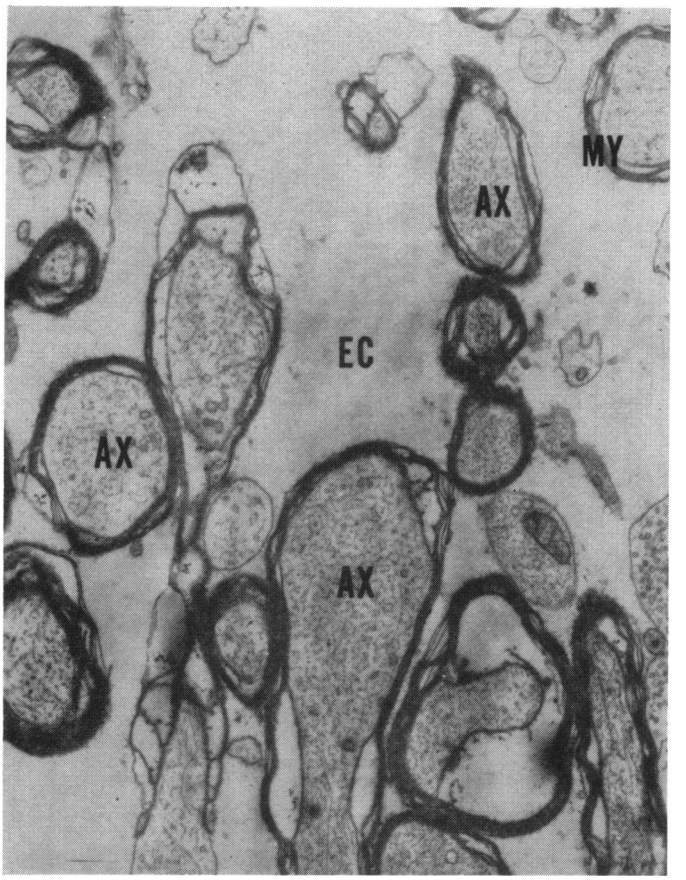

Fig. 2. Human white matter—edematous. There is enlargement of the extracellular space (E.C.). It may even overshadow the glial component of the swelling. There is axonal deformation (AX) and myelin disruption (MY). ×9740.

factors: 1) the extent of the fluorescein stain, 2) the intensity of the stain, 3) the presence of overt cerebral edema, 4) the presence of hemorrhages, and 5) the survival of the animals. Rabbits were used as the experimental animal and the edema-producing contrast medium (Hypaque) was injected into the left common carotid artery using a Harvard constant injection apparatus. The sodium fluorescein was given intravenously. The animals were broken down into two groups: 1) controls and 2) those premedicated with dexamethasone. It was apparent that the use of dexamethasone had a definite protective effect on the increased permeability produced under these experimental conditions. Figure 3 graphically summarizes the pertinent results. On the

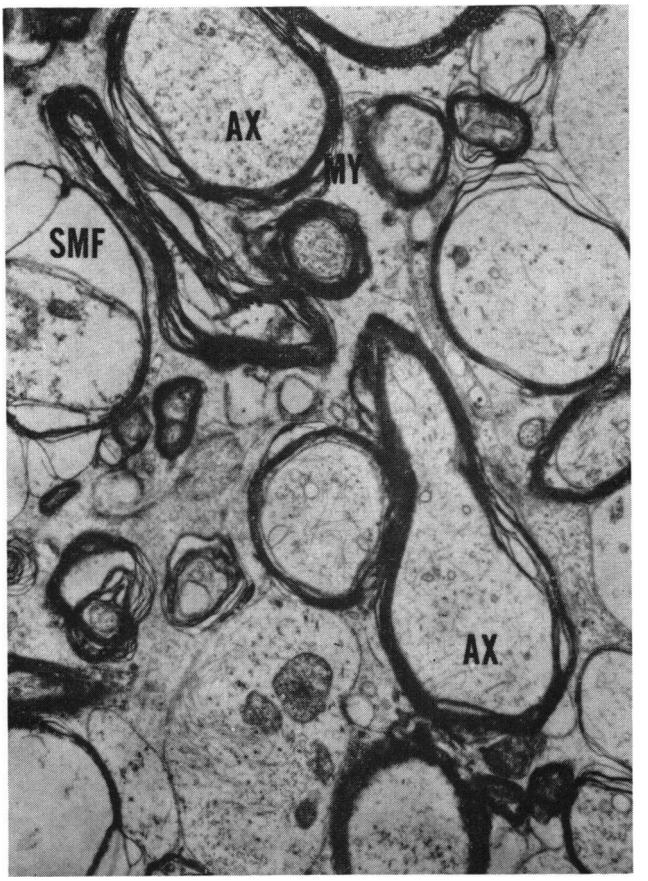

Fig. 3. Human white matter treated with dexamethasone. In contrast to the edema samples the extracellular space is not enlarged. The Axones (AX) have returned to a normal appearance and disruption of the myelin lamination (MY) is much less evident. Submyelin fluid and axonal deformation is rare. ×23.130.

ordinate are the number of animals and, on the abscissa, is a numerical estimate of change using the above-mentioned five factors. The first group had no premedication and obviously had a great deal of cerebral damage with a mortality rate of 24 per cent. Those that were premedicated with dexamethasone showed considerably less cerebral damage with a mortality rate of 6 per cent. The conclusion was that dexamethasone definitely has a protective effect against increased permeability produced by the intracarotid injection of Hypaque (90 per cent).

Dexamethasone has been used to help control the symptoms of cerebral edema in a large number of patients. Table I lists the lesions in the

TABLE I—RESPONSE TO DEXAMETHASONE THERAPY IN A SERIES OF 433 PATIENTS HAVING VARIOUS CAUSES OF EDEMA

Primary diagnosis	*No. cases*	*Marked improvement*	*Remarks*
Neoplasm	249	202	2 patients moribund 2 patients had subarachnoid blocks
Edema { operative	16	11	
Edema { postoperative	42	32	3 patients moribund
Closed head injury	63	35	
Subarachnoid hemorrhage	46	40	
Roentgen irradiation	8	8	
Intracerebral hematoma	6	0	
"Pseudotumor cerebri"	3	2	

patients in whom it has been possible, thus far, to evaluate the effects of dexamethasone alone, that is, without any other known beneficial form of therapy being given. The largest subgroup is comprised of patients with neoplasms. The reason for this is that they were easier to assess clinically than were some of the other patients. It should be noted that the patients included in this study are not the usual uncomplicated individuals with brain neoplasms but were those with extensive lesions who were believed preoperatively to have a great deal of associated edema. Many patients with neoplasms do not fall into this classification and hence were not given corticoids and were not included in this series. Table II lists the specific histological character of the neoplasms. There is nothing unusual about this grouping except that there is a comparatively large number of meningiomas and metastatic lesions, primarily because they are often associated with a fair amount of cerebral edema. The majority of patients were critically ill. Two hundred and twelve of the 249 had signs and symptoms of greatly increased intracranial pressure; 31 of them were comatose.

Table III shows the major signs and symptoms found in this series of patients as well as the response to therapy. Evidence of improvement was the prompt and continued relief, for the duration of treatment, of signs and symptoms of increased intracranial pressure and/or alleviation of neurological deficits. The onset of response was invariably within 12 to 18 hours following institution of therapy, and the maximum

TABLE II—HISTOLOGICAL CHARACTER OF NEOPLASMS IN 249 PATIENTS TREATED WITH DEXAMETHASONE

I.	Primary brain tumors		203
	Gliomas	154	
	Glioblastoma multiforme (91)		
	Astrocytoma (57)		
	Oligodendroglioma (6)		
	Meningiomas	41	
	Acoustic neurinoma	8	
II.	Secondary brain tumors		46
	Primary:		
	Lung	16	
	Genitourinary	11	
	Gastrointestinal	6	
	Pancreatic duct	1	
	Liver	1	
	Unknown	11	

neurological improvement was usually obtained within three to four days. Improvement was related to the location and to some extent to the histology of the neoplasm. Patients with metastatic tumors usually showed more improvement than those with glioblastomas, and patients with glioblastomas more than those with infiltrating astrocytomas. This correlates well with the severity of edema usually associated with these neoplasms. Returning to Table I, one can visualize the over-all response to therapy. Of the 249 patients with neoplasms 202 showed marked improvement. Some of them could not possibly have improved under any circumstances because they were so ill that nothing could have helped; in two patients there was extensive subarachnoid neoplastic implantation with block of the flow of cerebrospinal fluid.

There were 58 patients in whom there was evidence of edema developing during or immediately following the operation. The operations performed in this subgroup covered a wide spectrum of neurosurgical procedures including the removal of neoplasms, intracerebral hematomas, abscesses, and the obliteration of aneurysms. In 16 patients the therapy was begun during the surgical procedure because it was obvious that after resection of most or all of the neoplasm there was brain swelling to the extent that difficulty was encountered in closure of the dura. Three of these patients had large meningiomas involving

TABLE III—RESPONSE OF SYMPTOMS TO DEXAMETHASONE THERAPY IN 249 PATIENTS WITH BRAIN NEOPLASMS

Sign—symptom	*Present before treatment*	*Improved*	*Not improved*
Increased ICP*	207	189	18
Papilledema	125	57	68
Hemiplegia	87	64	23
Hemiparesis	66	49	17
Aphasia	43	37	6
Visual field defect	41	17	24
Sensory deficit	40	22	18

* Headache, nausea, vomiting, depression of sensorium.

veins leading to sagittal sinus, and another had removal of an arteriovenous malformation with extensive alteration of the venous drainage. Eleven of these 16 patients are included in the group of marked improvement because it was believed the postoperative difficulties were greatly lessened as a result of the use of dexamethasone. In 42 patients the drug was initiated following surgery when it became evident that the patient had either a progressive decline in the state of consciousness or an onset of focal neurological deficit. In 7 the depression of the sensorium had reached the point of coma when treatment was begun. Thirty-two of these 42 patients improved dramatically within 12 to 24 hours after initiating therapy. Three of the 10 patients who failed to improve were moribund at the time of instituting therapy. They were unresponsive and had fixed dilated pupils. Another patient, a man in extremely poor general condition following an evacuation of a large intracerebral abscess, also did not improve. Just why the other six patients did not improve is uncertain, but it is believed that it was related to the progressiveness of their basic lesion.

There were 63 patients with closed-head trauma. All were comatose for a period exceeding 24 hours when dexamethasone therapy was initiated. The diagnosis was severe cerebral concussion and contusion. None were believed to have appreciable space occupying intracerebral hematomas. In 35 of the 63 patients the state of consciousness improved remarkably; they were alert and oriented 24 hours after initiation of therapy.

There were 46 patients with spontaneous subarachnoid hemorrhage. The majority of these were secondary to ruptured intracranial aneurysms. All were obtunded with evidence of increased intracranial pressure at the time therapy was started. There was unquestionable symptomatic improvement in 40 of the 46 patients.

Eight patients developed distinct evidence of increased intracranial pressure during the course of deep roentgen therapy. In none was there evidence of increased pressure immediately prior to irradiation, and dexamethasone was given in an attempt to decrease the pressure. All eight had relief from nausea, vomiting, and headaches within a period of 24 hours.

There were six patients with large intracerebral hematomas and evidence of increased pressure treated with dexamethasone prior to surgery in an attempt to improve their very precarious condition. In none of them was there any evidence of improvement. However, all improved following surgical removal of the hematoma. Alas, it seems better to remove the clot!

There were three patients with "pseudotumor cerebri" who were treated. All three had signs and symptoms of increased intracranial pressure for which no explanation could be found. In two of the three there was definite improvement with therapy.

Complications

Because the majority of patients were treated with dexamethasone for a relatively short period of time the more common side effects associated with the use of corticosteroids were not encountered. However, several of the patients with neoplasms in whom treatment was continued after leaving the hospital developed moon facies. Hypertension was not observed in any of these patients. Serum electrolyte abnormalities were seldom encountered; when they did occur it was in the immediate postoperative period and hence difficult to ascribe to dexamethasone therapy. The catabolic and antifibroblastic action of the glucocorticoids did not appear to interfere with wound healing although there were seven patients in whom wound healing was delayed. Four of these seven patients had previous operations, and two of the four had previous deep roentgen therapy with definite irradiation damage of the scalp. Slow wound healing was not a pertinent complication in patients with normal skin, but the possibility of delayed healing in the

presence of an abnormal, irradiated scalp is present.

The incidence of wound infection was not affected by the use of dexamethasone. Two patients with evidence of severe cerebral edema in whom intracerebral abscesses were drained received dexamethasone. In neither was there evidence of dissemination of the infectious process.

Acute gastrointestinal ulceration or bleeding occurred in four patients. In only one of them was such a lesion apparent during life. This was a moribund patient who had hematemesis just prior to death. In two of the patients gastrointestinal ulcerations were found at autopsy and, in a fourth patient, blood was found in the large bowel at autopsy but no bleeding source could be found. An additional patient with a known duodenal ulcer had an exacerbation of "ulcer symptoms" while on dexamethasone. He had no evidence of bleeding. Most of the patients received anticholinergic medication concomitantly with dexamethasone. This undoubtedly helped in alleviating some of the G-I complications.

There are two additional phenomena encountered in this series which should be listed with the complications. The first is the masking of postoperative hematomas. This occurred in three patients. Two of them did well for several hours following surgery, but then developed progressive lethargy and hemiparesis. Treatment with corticoids was associated with a prompt return to normal of their state of consciousness and definite improvement of their hemiparesis. However, the clue to the underlying process in these patients was the fact that the return of motor function reached a plateau and, in one patient, the disability returned to its previous intensity as soon as the dosage of corticoid was diminished from 4 mg. every 6 hours to 2 mg. every 8 hours. All three patients made excellent recoveries following removal of hematomas. Their initial improvement can be explained by relief of the edema adjacent to the clots.

A second related phenomenon is that of exacerbation or perhaps even initiation of cerebral edema with rapid reduction or sudden withdrawal of corticosteroids in patients who have been maintained on high dosages for a week or longer. The explanation probably lies in the fact that there is a marked diminution of the output of endogenous glucocorticoids secondary to a block, by dexamethasone, of ACTH production. The decline in endogenous production can be rapid. Two patients in this series, in whom daily 17-hydroxycorticosteroids were determined, had essentially complete disappearance of these compounds from their

urine within 48 hours after starting dexamethasone. Such patients have a relative adrenal insufficiency and, with prolonged therapy, the responsiveness of the adrenal gland to ACTH is diminished. With a rapid reduction, or discontinuation, of exogenous corticoid, the patients may then have return of cerebral edema.

Summary

A review is given of experience with the use of dexamethasone in the treatment of cerebral edema. This synthetic adrenal corticoid seems to be an effective agent when used for this purpose. Although dexamethasone therapy is associated with some complications, these are far outweighed by its benefits.

It is believed the proper time for the use of dexamethasone is not in the routine craniotomy for glioma—it simply is not needed—but it is of value: 1) in the patient with increased intracranial pressure in whom there is reason to procrastinate a day or two, hoping the patient will then be in better condition for the craniotomy; 2) patients with recurrent neoplasms associated with increased intracranial pressure due to cerebral edema can be benefitted for many months; 3) patients with brain swelling that develops during the surgical procedure can be given intravenous dexamethasone during surgery, followed by intramuscular therapy, and have their postoperative course immeasurably ameliorated; and 4) in fact, any patient with a problem of cerebral edema can be benefitted because these corticoids do relieve symptoms attributable to edema.

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